REMARKS

Claims 1-14 are presently pending in the instant Application. In the instant Amendment, Claims 3-4 have been canceled, without prejudice, Claims 1 and 6 have been amended, and new Claim 15 has been added. Support for amended Claims 1 and 6, and for new Claim 15 can be found generally throughout the instant Specification, and particularly on page 2, lines 26-32; page 3, lines 1-4; and in Claims 1-5 as originally filed.

Furthermore, on page 6, paragraph 6 of the outstanding office action, the Examiner has admitted that pending Claim 10 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. § 112, first paragraph, set forth in the office action, and to include all of the limitations of the base claim and any intervening Claims. It is respectfully submitted that new Claim 15 complies with the Examiner's admission, and should be allowed to issue.

The Invention is Enabled

Claims 1-2, 5, 6-14 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner has admitted the instant Specification is enabled for a pH level around 8.5 to 9.0. However, it is the Examiner's belief that the instant Specification does not provide enablement for any pH level. In particular, the Examiner has asserted that the instant Invention is directed towards a process for detecting C-peptide containing impurities in a sample of insulin or a derivative by a non-radioactive assay. However, the Examiner believes that in the third paragraph of page 3 of the instant Application, Applicant stressed that "due to the physical properties of the test batch step samples, the antibodies used must interact with the antigens with sufficient affinity at a pH of about 8.5 – 9.0." Moreover, the Examiner believes working

examples and other commercial assays compared by Applicant, e.g. example 1, RIA kit, cat #HP1-15K at page 7) also indicate that a pH of about 8.5-9.0 is necessary for the instant Invention. Hence, it is the Examiner's opinion that the scope of the current invention can operate at a limited pH level, namely pH of about 8.5 – 9.0, not at all pHs.

This rejection is respectfully traversed. Claim 1 has been amended to be directed towards, *inter alia*, a process for detecting or determining a C-peptide-containing impurity comprising human C-peptide, monkey C-peptide, or a mixture thereof, in a sample of recombinantly produced human insulin or a derivative thereof, by a non-radioactive assay, wherein the process is performed at a pH of about 8.5 to about 9.0. Support for this amendment can be found on page 3, lines 5-13 of the instant Specification. Hence, this rejection should be withdrawn.

The Invention is Definite

Claim 6 has been rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the Invention. The Examiner has asserted that "and" recited in line 5 of Claim 6 should be changed to "or" for correct Markush recitation.

This rejection is respectfully traversed. Claim 6 has been amended to recite a Markush grouping having the correct format. Hence, this rejection should be withdrawn.

The Invention is Unobvious

Claims 1-2, 6-9, 11-12 and 14 have been rejected under 35 U.S.C. §103(a) as being unpatentable in light of the teachings of Iizuka *et al.* (Biomedical Research 11:417-423 (1990))

in view of the teachings of European patent application EP 0484961 (the '961 application) and teachings of the U.S. Patent 5,811,266 (the '266 patent). The Examiner has asserted that Iizuka *et al.* teach measuring human C-peptide containing sample by mixing the sample with a first antibody specifically recognizing the C-peptide, and a tracer, e.g. C-peptide, and a second radioiodinated I^{125} antibody bead recognizing the first anti-C-peptide for determining the human C-peptide which is a degradation product from processing proinsulin. However, the Examiner has admitted that Iizuka *et al.* do not teach (1) using recombinant human insulin as the sample, and (2) a non-radioactive assay to determine the C-peptide in a sample.

The Examiner has also asserted that the '266 patent teaches the use of a genetic recombinant method to produce human insulin to meet the great demand and research in diabetes (col. 3, lines 20-45 and claim 1). Moreover, the Examiner believes that the '961 application teaches labeling of antibodies recognizing the antibody specific for the C-peptide for an efficient assay. The Examiner has also asserted that the '961 application points out problems with radioactive safety of an operator and disposal of the isotope for an immunoassay, and thus, includes an alternative labeling technique, e.g. non-radioactive fluorescence labeling. The Examiner also believes that the acridinium ester moiety recited in Claim 9 of the instant Application as a tracer is a type of fluorescent substance encompassed by the '961 application. Hence, it is the Examiner's opinion that it would have been obvious to one of ordinary skill in the art at the time the instant Invention was made to have provided the assay of Iizuka *et al.* to detect the purity of the genetically produced human insulin as taught by the '266 patent for the great demand of human insulin and its quality control in diabetes research, and labeling another

antibody recognizing the first antibody specific for the C-peptide with a non-radioactive labeling as an alternative substitute for radioactive I^{125}, for safe operation and disposal.

This rejection is respectfully traversed. Initially, it is respectfully submitted that the Examiner's interpretations of Iizuka *et al.* is not correct. In particular, contrary to the Examiner's assertion, the second antibody bead that recognizes human C-peptide is not radioactive. Rather, the human C-peptide tracer is labeled with I^{125}. Indeed, in the first column of page 419 of Iizuka *et al.*, they make clear:

> Radioiodination of tyrosylated human C-peptide with ^{125}I-Na was carried out by a modified chloramines T method. Labelled peptide was purified by gel filtration on a sephadex G-25 column using 1.0 M acetic acid or by reversed phase HPLC on a TSK Gel ODS-120T column (solvent system; 1% AcOH/CH_3CN). The solvent of HPLC was changed by a linear gradient of 30% CH_3CN to 37.5% CH_3CN for 30 min. A single pink fraction purified by gel filtration and three peak fractions obtained by reversed phase HPLC were examined.

Iizuka *et al.* further explain the procedure for producing the second antibody coated beads. That procedure though, reproduced below, makes no mention of the use of a radioactive isotope. Rather, radiolabeled anti-goad IgG-Fc mouse monoclonal antibody was utilized merely to quantify the amount of second antibody coated onto each bead:

> *Preparation of Second Antibody coated Beads*
>
> One-fourth inch beads were washed by 5% SCAT 20X-PS (non-phosphoric detergent, Daiichi Kougyou Seiyaku, Kyoto, Japan) and distilled water, and then coated with anti-goat IgG-Fc mouse MCA (second antibody) in 1 mM phosphate buffer (pH 6.4) according to a modified procedure of Catt and Tregear (1). Coated beads were washed with distilled water, protected by 0.5% BSA in 10 mM phosphate buffer (pH 7.4) and dried *in vacuo*. ***The amount of second antibody coated onto a bead was examined by binding of ^{125}I-anti-goad IgG-Fc mouse MCA.*** Beads were coated with 5 μg

of second antibody.

(Iizuka *et al.*, p. 419, second column (emphasis added)).

Moreover, as the Examiner has admitted, the '266 patent teaches the use of a genetic recombinant method to produce human insulin. Consequently, the '266 patent provides no teachings regarding a method or process for assaying the purity of insulin produced with a genetic recombinant method set forth therein. Hence, it is respectfully submitted no teaching or motivation exists in the '266 patent to combine its teachings with any of the references the Examiner has cited in making this rejection.

Similarly, no motivation or suggestion to combine any of the remaining references as the Examiner has done in making this rejection. In particular, as the Examiner has clearly admitted, Iizuka *et al.* teach the use of a ***radioimmunoassay***, and does not teach assaying a sample that contains recombinant human insulin. Rather, as it is made clear in the title and abstract of Iizuka *et al.*, the sample is serum or urine, and neither inherently contains recombinant human insulin.

In addition, '961 application teaches two methods for measuring human C-peptide. One method utilizes ***two*** antibodies that recognizes human C-peptide, ***wherein in each antibody recognizes a separate site on the human C-peptide***. In particular, on page 2, lines 23-26 of the '961 application, it is made clear that:

> In one aspect of the present invention, there is provided a method of measuring human C-peptide which comprises the steps of (a) contacing [sic] a sample containing human C-peptide with a first antibody specifically recognizing human C-peptide and a second antibody specifically recognizing human C-peptide ***at a site thereof different from the site recognized by the first antibody***...(emphasis added)."

It is respectfully submitted that such a method is entirely ***unrelated*** to the instant Invention, and indeed unrelated to the teachings of any of the other references the Examiner has cited in this rejection, particularly since it requires the use of two antibodies having human C-peptide as an immunogen, wherein each antibody binds to a different site on human C-peptide.

The other method set forth in the '961 application involves a competitive assay for measuring human C-peptide that utilizes an antibody ***specific for human C-peptide***. However, amended Claim 1 above is directed towards a process for detecting or determining a C-peptide-containing impurity comprising human C-peptide monkey C-peptide or a mixture thereof, comprising, *inter alia*, an antibody specific for a C-peptide containing impurity comprising human C-peptide or monkey C-peptide. Moreover, on page 2, lines 26-32; and page 3, lines 1-4 of the instant Specification, it is clearly explained that:

> ....The object of the present invention was to produce antibodies that can be applied in an immunoassay to quantify insulin C-peptide containing impurities in a final pure insulin preparation obtained in a specific purification batch ("end probes") of HI (INSUMAN™), HIA1 (GLARGINE™), and HIA2 production, as well as in in-process batch step samples of the three insulin variants.
>
> ***The antibodies should show affinity to isolated monkey C-peptide*** and prepoinsulin ("PPI"), but they should also be able to bind to model compounds, such as PPI, ***human and/or monkey C-peptide***, HI reduced/alkylated, HI cleaved with endoproteinase Asp-N at the EDP, HIA2 C-peptide, and HIA2 PPI, which are designed to reflect a panel of putative side products and impurities that can be anticipated in the industrial recombinant production of insulin.

None of the references the Examiner has cited teach or imply the use of the antibody that recognizes ***monkey C-peptide***, among a variety of immunogens it recognizes. Hence, for reasons

discussed above, no motivation or suggestion exists in any of these references to combine their teachings as the Examiner has done in making this rejection. Furthermore, no combination of these references will ever result in a process for detecting or determining a C-peptide-containing impurity comprising human C-peptide or ***monkey C-peptide***. Hence, it is respectfully submitted that the amended Claim 1 as well as Claims dependent thereto are clearly unobvious, and this rejection should be withdrawn.

Furthermore, Claim 3 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Iizuka *et al.* in view of the teachings of the '266 patent, the '961 application, and further in view of the teachings of U.S. Patent 6,444,641 (the '641 patent). The Examiner's interpretations of the teachings of Iizuka *et al.*, the '266 patent, and the '961 application are discussed above. The Examiner has admitted that none of these references specifically teach the performance of the assay at a pH level around 8.5 – 9.0. However, the Examiner believes that Table 5 of the '641 patent discloses the solubility of human C-peptide at a pH of 8.02 – 9.0. Hence, it is the Examiner's opinion that it would have been obvious for one of ordinary skill in the art at the time the instant Invention was made to have provided the non-radioactive assay of the instant Invention for detecting human C-peptide with an optimal pH level around 8.5 – 9.0, as taught by the '641 patent because, in the Examiner's opinion, it is known that a certain pH level would be necessary, i.e. soluble condition, for performing the immunoassay.

It is respectfully pointed out to the Examiner that in this Amendment, Claim 3 has been canceled, without prejudice. Hence, this rejection is MOOT with respect to Claim 3. However,

this rejection is respectfully traversed with respect to amended Claim 1. For reasons discussed above, the instant Invention as set forth in the amended Claim 1 is unobvious in light of a combination of the teachings of Iizuka *et al.* with the teachings of the '266 patent and the '961 application. Combining the teachings of these references with the teachings of the '641 patent does not render the subject matter of amended Claim 1 obvious. In making this rejection, the Examiner has asserted that Table 5 of the '641 patent discloses the solubility of C-peptide is 8.02-9.0. However, Table 5 does not disclose the solubility of C-peptide at various pH levels, but rather sets forth a summary of solubility data for ***B29-N^{ϵ}-$Arg^{A0}Gly^{A21}Arg^{B31}Arg^{B32}$-Myristoyl Human Insulin Analog***. In addition, it is explained in lines 60-67 in column 28 of the '641 patent that the solubility of this human insulin analog ***is not limited*** to a pH of around 8.02 – 9.0:

> Table 5 presents the data that was obtained in the solubility study of B29-N^{ϵ}-$Arg^{A0}Gly^{A21}Arg^{B31}Arg^{B32}$-Myristoyl Human Insulin Analog and FIG. 1 illustrates the same data in graphical form. The data indicates that the solubility of the acylated human insulin analog of this study decreases significantly when pH drops below 8.66 ***and does not increase until the pH decreases below about a pH of 4.5*** (emphasis added).

Hence, contrary to any assertion of the Examiner, amended Claim 1 is unobvious to one of ordinary skill in the art in light of any combination of these references.

Claims 4 and 13 have also been rejected under 35 U.S.C. § 103 (a) as being unpatentable of the teachings of Iizuka *et al.*, the '266 patent and '961 application, and further in view of the teachings of Naithani *et al.* (Fed. Rep. Ger. International Congress Series 468:94-98 (1979)). In making this rejection, the Examiner has admitted that Iizuka *et al.*, the '266 patent, and the '961 application, do not disclose antibodies specifically recognizing monkey C-peptide. The

Examiner has asserted though that Naithani *et al.* teach syntheses of monkey C-peptide and its derivatives. It is the Examiner's position that it would have been obvious for one of ordinary skill in the art at the time the instant Invention was made, to have used the conventional antibody technique to generate antibody specific for monkey C-peptide because, in the Examiner's opinion, the Board of Patent Appeals and Interferences has taken the position that once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious. In support of this opinion, the Examiner has cited *Ex Parte Ehrlich*, 3 USPQ2d 1011 (PTO Bd. Pat. APP. & Int. 1987); *Ex parte Sugimoto*, 14 USPQ2d 1312 (PTO. Bd. Pat. APP. & Int. 1990).

In the instant Amendment, Claim 4 has been canceled, without prejudice. Hence, this rejection with respect to Claim 4 is MOOT. However, this rejection is respectfully traversed with respect to amended Claim 1 and Claim 13. As explained above, the instant Invention is unobvious to one of ordinary skill in the art in light of any combination of the teachings of the teachings of Iizuka *et al.*, the '266 patent and '961 application. The addition of the Examiner's assertion that the manufacture of a monoclonal antibody having monkey C-peptide as an immunogen is *prima facie* obvious in to the other cited no way renders the instant Invention obvious. MPEP § 2141 clearly states:

> When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:
>
> (A) The claimed invention must be considered as a whole;
>
> (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

Initially, it appears that in making this rejection, the Examiner has not considered the claimed invention as a whole, but rather is considering only elements of the invention. The Examiner believes that asserting that an antibody having monkey C-peptide as an immunogen is *prima facie* obvious, and thus makes the instant Invention obvious in light of the teachings of the references cited. However, an antibody is only one element of the instant Invention. Moreover, antibody used in a process of the instant Invention binds to compounds other than monkey C-peptide. In particular, an antibody used in a process of the instant Invention "*...should show affinity to* ***isolated monkey C-peptide and prepoinsulin*** ("PPI"), but ***they should also be able to bind to model compounds***, such as ***PPI, human and/or monkey C-peptide*** (emphasis added)." No combination of any of the references cited by the Examiner in this rejection teaches or suggests a process for detecting or determining a C-peptide-containing impurity comprising human C-peptide, monkey C-peptide, or a mixture thereof, in a sample of recombinantly produced human insulin or a derivative thereof, that utilizes an antibody having such properties. Furthermore, as the Examiner has admitted, Iizuka *et al.* teach a radioimmunoassay for the presence of ***human*** C-peptide in serum or urine (and thus is non-recombinant) that utilizes a radioactive isotope; the '266 patent teaches the use of a genetic recombinant method to produce human insulin; and the '961 application is directed towards methods for measuring ***human*** C-peptide. Hence even if, merely for the sake of argument, the Examiner's assertion that a

monoclonal antibody having monkey C-peptide as an immunogen is *prima facie* obvious, which in no way is admitted, such an antibody by itself would have ***nothing*** to do with the teachings of the references cited. Thus, contrary to the Examiner's assertion, no motivation or suggestion suggestions in any of these references to combine them as the Examiner has done in making this rejection. Indeed, it is respectfully submitted that in making all of these rejections under 35 U.S.C. § 103(a), the Examiner has utilized impermissible hindsight in an unsuccessful attempt to construct the instant Invention from these references. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure." [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]." *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). In the light of the above, it is respectfully submitted that this rejection be withdrawn, and the Claims be allowed to issue.

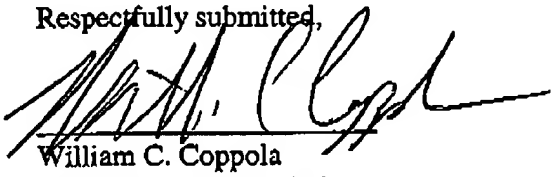
Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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